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## PHYSICIANS' DESK REFERENCE®

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## EXHIBIT A

## 880/PHYSICIANS' DESK REFERENCE®

## Ciba Self-Medication, Inc.—Cont.

delivery system of SLOW FE is designed to maximize the release of ferrous sulfate in the duodenum and the jejunum where it is best tolerated and absorbed. SLOW FE has been clinically shown to be associated with a lower incidence of constipation, diarrhea and abdominal discomfort when compared to an immediate release iron tablet<sup>1</sup> and a leading sustained release iron capsule.<sup>2</sup>

## FORMULA

Each tablet contains: Active Ingredient: 160 mg dried ferrous sulfate USP, equivalent to 50 mg elemental iron. Inactive Ingredients: cetostearyl alcohol, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyacrylate 80, talc, titanium dioxide, yellow iron oxide, FD&C Blue #2 aluminum lake.

## DOSAGE

**ADULTS**—one or two tablets daily or as recommended by a physician. A maximum of four tablets daily may be taken. **CHILDREN**—one tablet daily. Tablets must be swallowed whole.

## WARNING

The treatment of any anemic condition should be under the advice and supervision of a physician. As oral iron products interfere with absorption of oral tetracycline antibiotics, these products should not be taken within two hours of each other. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Keep this and all drugs out of the reach of children. Close bottles tightly. Contains iron, which can be harmful or fatal to children in large doses. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Tamper-Evident Packaging.

## HOW SUPPLIED

Blister Packages of 30 and 60, and bottles of 100 supplied in Child-Resistant packaging. Do not store above 30°C (86°F). Protect from moisture.

## REFERENCES

1. Brock C et al. Adverse effects of iron supplementation: A comparative trial of a wax-matrix iron preparation and conventional ferrous sulfate tablets. *Clin Ther.* 1985; 7:1-VI.
2. Brock C, Curry H. Comparative incidence of side effects of a wax-matrix and a sustained-release iron preparation. *Clin Ther.* 1985;7:492-496.

Shown in Product Identification Guide, page 308

## SLOW FE® WITH FOLIC ACID

(Slow Release Iron - Folic Acid)

OTC

## DESCRIPTION

Slow Fe + Folic Acid delivers 50 mg. elemental iron (160 mg. dried ferrous sulfate) using the unique wax matrix delivery system described above (for SLOW FE® Slow Release Iron Tablets) plus 400 mcg. folic acid.

Provides women of childbearing potential with the daily target level of folic acid to reduce the risk of neural tube birth defects. These birth defects are rare, but serious, and occur within 28 days of conception, often before a woman knows she's pregnant.

## FORMULA

Each tablet contains: Active Ingredients: 160 mg. dried ferrous sulfate, USP (equivalent to 50 mg. elemental iron) and 400 mcg. folic acid. Inactive Ingredients: cetostearyl alcohol, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyacrylate 80, talc, titanium dioxide, yellow iron oxide.

## DOSAGE

**ADULTS**—One or two tablets once a day or as recommended by a physician. A maximum of two tablets daily may be taken. **CHILDREN UNDER 12**—Consult a physician. Tablets must be swallowed whole.

## WARNING

The treatment of any anemic condition should be under the advice and supervision of a physician. As oral iron products interfere with absorption of oral tetracycline antibiotics, these products should not be taken within two hours of each other. Intake of folic acid from all sources should be limited to 1000 mcg. per day to prevent the masking of Vitamin B<sub>12</sub> deficiencies. Should you become pregnant while using this product, consult a physician as soon as possible about good prenatal care and the continued use of this product. If you are already pregnant or nursing a baby, seek the advice of a health care professional before using this product. KEEP THIS PRODUCT AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Contains iron, which can be harmful or fatal to children in large doses. In case of accidental overdose, contact a physician or a poison control center immediately.

## HOW SUPPLIED

Blister packages of 20 supplied in Child-Resistant packaging. Do not store above 30°C (86°F). Protect from moisture.

## CHILD-RESISTANT

Blister packaged for your protection. Do not use if individual seals are broken.

Distributed by: Ciba Self-Medication, Inc.

Woodbridge, NJ 07095

Tablets made in Great Britain

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Shown in Product Identification Guide, page 308

## TRANSDERM SCOP®

(trans-derm scop®)

scopolamine

Transdermal Therapeutic System

Programmed delivery in vivo of 0.5 mg of scopolamine over 3 days

## Prescribing Information

## DESCRIPTION

The Transderm Scop patch is a circular flat disc designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Clinical evaluation has demonstrated that the patch provides effective antiemetic and antinausea actions when tested against motion-sickness stimuli in adults. The Transderm Scop patch is a film 0.2 mm thick and 2.5 cm<sup>2</sup>, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminumized, polyester film; (2) a drug reservoir of scopolamine, mineral oil, and polyisobutylene; (3) a microporous polypropylene membrane that controls the rate of delivery of scopolamine from the patch to the skin surface; and (4) an adhesive formulation of mineral oil, polyisobutylene, and scopolamine. A protective peel strip of silicone-coated polyester, which covers the adhesive layer, is removed before the patch is used. The inactive components, mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not released from the system.

## Cross section of the patch:



**Release-Rate Concept:** The Transderm Scop patch contains 1.5 mg of scopolamine. The patch is programmed to deliver 0.5 mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the patch. An initial priming dose of scopolamine, released from the adhesive layer of the patch, saturates the skin binding sites and rapidly brings the plasma concentration of scopolamine to the required steady-state level. A continuous controlled release of scopolamine, which flows from the drug reservoir through the rate-controlling membrane, maintains the plasma level constant.

## CLINICAL PHARMACOLOGY

The sole active agent of Transderm Scop is scopolamine, a belladonna alkaloid with well-known pharmacological properties. The drug has a long history of oral and parenteral use for central anticholinergic activity, including prophylaxis of motion sickness. The mechanism of action of scopolamine in the central nervous system (CNS) is not definitely known but may include anticholinergic effects. The ability of scopolamine to prevent motion-induced nausea is believed to be associated with inhibition of vestibular input to the CNS, which results in inhibition of the vomiting reflex. In addition, scopolamine may have a direct action on the vomiting center within the reticular formation of the brain stem. Applied to the postauricular skin, Transderm Scop provides for a gradual release of scopolamine from an adhesive matrix of mineral oil and polyisobutylene.

## INDICATIONS AND USAGE

Transderm Scop is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The patch should be applied only to skin in the postauricular area.

**Clinical Results:** Transderm Scop provides antiemetic protection within several hours following application of the patch behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 76% reduction

in the incidence of motion-induced nausea and vomiting. Transderm Scop provided significantly greater protection than that obtained with oral dimenhydrinate.

## CONTRAINDICATIONS

Transderm Scop should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

## WARNINGS

Transderm Scop should not be used in children and should be used with special caution in the elderly. See PRECAUTIONS.

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

## PRECAUTIONS

## General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scop should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

## Information for Patients

Since scopolamine can cause temporary dilation of the pupil and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the patch.

Patients should be advised to remove the patch immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils). Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

## Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

## Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scop should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

## Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scop is administered to a nursing woman.

## Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scop should not be used in children because it is not known whether the patch will release an amount of scopolamine that could produce serious adverse effects in children.

## ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scop is dryness of the mouth. This occurs in about two thirds of patients on drug. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of patients on drug. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed. The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scop: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rash; and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

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